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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Supplemental Examiner's Answer

The reply brief filed 3/12/09 is acknowledged. The appellant provide additional arguments, which are similar to those introduced during the prosecution but are they not present in the Brief on Appeal. The arguments will be addressed below.

Claims 113, 116, 117, 119, 120, 123, 124 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Low et al.* (Nat Biotech 1999;17:37-41, IDS), in view of *Schachter et al.* (Cancer Biother Radiopharm 1998 Jun;13:155-64).

The appellant points to evidence first introduced to the record on 5/27/2007 in a response to a final action.

Evidence:

Original Exhibit B: Chow et al. (abstract, Leuk Lymphoma,2003), who teaches two chemical compounds capable of exerting synergistic as well as antagonistic effects on proliferation, apoptosis and disruption of mitochondrial membrane potential in a leukemic cancer cell line.

Original Exhibit C: Budman et al. (abstract, Anticancer Drugs 2002), who teaches synergistic and antagonistic combinations of chemotherapeutic drugs in three human prostate cancer cell lines through comparison of combination index for each combination of various compounds on cancer cell.

Original Exhibit D: Dasmahapatra et al. (Clin Cancer Res 2004), who teaches two specific chemotherapeutic compounds have synergistic effect on killing cancer cells in both prostate and lung cancer.

The appellant argues that these references provide evidence of the unpredictability in the art, and that the examples demonstrate that combinations of anti-tumor agents may work synergistically, antagonistically, or may act without any measurable effect.

The evidence and arguments have been fully considered but found not sufficient to obviate the rejection of record for reasons following:

1. The references provide confirmation in terms of motivation for combining different therapeutic regimens in cancer treatment. For example, *Dasmahapatra* states, "COMBINING ANTIEOPLASTIC AGENTS HAS PROVEN TO RESULT IN SEVERAL EFFECTIVE REGIMENS IN CANCER THERAPY. CURRENT CYTOTOXIC REGIMENS EMERGED FROM EFFORTS TO MATCH AGENTS WITH NONOVERLAPPING TOXICITY TO THE HOST. IN CONTRAST, COMBINING AGENTS, WHICH ACT AT DISTINCT POINTS IN A SIGNAL TRANSDUCTION PATHWAY MIGHT ALLOW MORE EFFICIENT BLOCKADE OF THAT PATHWAY'S ACTIVATION...WE DOCUMENT HERE THAT INDEED PERIFOSINE AND UCN-01 SYNERGISTICALLY INHIBIT PROLIFERATION OF PC-3 PROSTATE CARCINOMA CELLS" (col 2, page 5243). Apparently, there are needs and more than one strategy to design a therapeutic combination regimen.

2. *Dasmahapatra* provides reasoning for combine and reports synergistic effect between two chemotherapeutic compounds. All three references have shown synergistic effects when combining certain chemotherapeutic compounds. Apparently,

synergy and additive is a predominant phenomenon when combining two or more chemotherapeutic drugs *wisely* designed by an ordinary skilled in the art.

3. The references illustrated that the skilled in the art were fully aware that the combination of chemical compounds may work synergistically, antagonistically, or may act without any measurable effect. Determining such potentially different effects was routine in the pertinent art. Any experimentation for affirmation of a combination effect would be considered routine experimentation such as those taught by *Budman*, who measures synergy and antagonism by the combination index for each combination.

4. In biochemistry and pharmacology, "antagonism" refers to interference in the physiological action of a chemical substance by another having *a similar structure*. This is consistent with the three references provided by the appellant: all of them deal with the combination between two chemical compounds having similar structure or targeting the same signaling pathway. For example, both Ara-C and 2-CdA are nucleoside analogues (*Chow et al.*) that mimic physiological nucleosides in terms of uptake and metabolism.

This is not the case for instant rejections, wherein the references relied on are not a combination between two chemotherapeutic agents, but between a routine chemotherapeutic regimen and a bacteria therapy via a very different approach for killing cancer cells. No structural similar compounds are involved between the two approaches nor do they target the same signaling pathway. Hence, it is unlikely an antagonistic effect would occur when one combines the two.

Accordingly, for reasons of record and *supra*, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the attenuated tumor-targeted mutant *Salmonella* therapy as taught by *Low et al.* with the cisplatin chemotherapeutic regimen as taught by *Schachter et al.* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention for additive therapeutic effects. Given the state of the art that the conventional therapy alone was often insufficient in combating cancer, given the skilled was constantly searching for new means to improve conventional cancer treatment, and given that each of the cited references teaches an agent that is effective in treating melanoma, one would have had a reasonable expectation of success when combining the two. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

The appellant argues that they have shown a synergism between attenuated *Salmonella* and cytoxan, which cannot be predicted by the combined teachings in view of the results of mitomycin C in the specification.

In response, it is reiterated mitomycin C alone does not have much of an effect compared to the control (figure 40) and thus one would not have expected any significant change when combined with the *Salmonella*.

As to the asserted "synergistic effect" between cytoxan and attenuated *Salmonella* from expected "55-60% to 80%", the appellant's mathematics does not appear to be accurate. According to the data presented in figure 39 of the specification, the rates of tumor inhibition at day 25 and 30 are as follows:

Treatment	Rate of Inhibition (%) (as shown)	Expected Additive Effect (day 25)	Rate of Inhibition (%) (estimate)	Expected Additive Effect (day 30)
Cytoxan 200mg	35		25	
Salmonella VNP20009	45	35+45=80	50	25+50=75
Cytoxan 150 + VNP20009	74	74	82	82
Cytoxan 200 + VNP20009	83	83	87	87

Hence the effect may be better described as additive and expected at day 25, and slightly more than additive at day 30. Considering biological responses do not often follow strict mathematics, variations are seen more often than not between and within experiments, the degree of differences in the table among different groups at day 30 would still be considered as within a reasonable expectation, not entirely unexpected.

Even assuming *arguendo*, the synergy exists at day 30, it was achieved by a particular drug cytoxan with a particular strain (VPN20009) of *Salmonella*, and thus the scope of the claims should limited to the particular combination. This is not the case for instant claims, where none is limited to the particular combination, and claim 123 broadly embraces any anti-cancer compound. The court has determined, "WHETHER THE UNEXPECTED RESULTS ARE THE RESULT OF UNEXPECTEDLY IMPROVED RESULTS OR A PROPERTY NOT TAUGHT BY THE PRIOR ART, THE "OBJECTIVE EVIDENCE OF NONOBVIOUSNESS MUST BE COMMENSURATE IN SCOPE WITH THE CLAIMS WHICH THE EVIDENCE IS OFFERED TO SUPPORT." IN OTHER WORDS, THE SHOWING OF UNEXPECTED RESULTS MUST BE REVIEWED TO SEE IF THE RESULTS OCCUR OVER THE ENTIRE CLAIMED RANGE. *IN RE CLEMENS*, 622 F.2D 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)" ((MPEP 716.02(d), emphasis added)).

Moreover, following the desire for achieving additive effect as taught by the combined teaching would bring about the synergistic effect.

Accordingly, for reasons of record and *supra*, the rejection stands.

The appellant went on to argue that the examiner fundamentally misunderstand the mechanism of action of the attenuated tumor-targeted *Salmonella* and the teaching of Jirillo, which does not follow the same underlying principle as does the biotherapy taught by Schachter.

The argument has been fully considered but found not persuasive. It is in the context of immune regulation that the Office concluded that the attenuated *Salmonella* taught by *Low* has similar underlying principle as does the biotherapy taught by *Schachter* in treating cancer because regardless what underlying principles they may be, and what side effects the bacteria may assert, it is undeniable that both *Low* and *Jirilo* had safely used the attenuated *Salmonella* for treating tumor. Since *Jirilo* proves that the attenuated *Salmonella* could enhance immune responsiveness in cancer patients, it would likely to be the case for *Low* even though he did not explicitly teach such. The Office does not suggest that the attenuated bacteria is an equivalent of cytokines use by *Schachter et al*, rather, *Schachter et al* is relied on for a general desirability of combining a new therapeutic regimen with an existing conventional one. In a clinical setting, the skilled rarely uses only one drug/one type of therapy in a cancer therapeutic regimen, combining chemotherapy with radiotherapy or newly developed cytokine, bacteria, gene therapy often was and have been the routine.

Accordingly, for reasons of record and *supra,* the rejection stands.

Claims 115, 121, 122 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Low et al.* (Nat Biotech 1999;17:37-41, IDS), in view of *Schachter et al.* (Cancer Biother Radiopharm 1998 Jun;13:155-64) as applied to claims 113, 116, 117, 119, 120, 123, 124 above, further in view of *Pawelek et al.* (Cancer Res 1997;57:4537-44, IDS).

The appellant alleges that Pawelek is a new ground of rejection. This is false. This ground of rejection has been on record since June 28, 2007.

For the above reasons, it is believed the rejections should be sustained.

Respectfully submitted

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